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Do we need hair follicle stem cells and hair follicle neogenesis to cure common hair loss disorders?

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Few concepts have ingrained themselves as quickly with physicians who treat hair loss as the vague notion that to cure the common causes of alopecia and effluvium, somehow, one needs to be able to manipulate hair follicle stem cells, either by forcing them to "behave" in a manner that clinically and cosmetically desired hair growth results are obtained, or by injecting them so as to induce the formation of new hair follicles. It has attained almost the status of conventional wisdom that injecting just the right kind of stem cells will usher in a brave new age of iatrogenic hair follicle neogenesis, where newly created hair follicles (either generated directly in adult skin or even *in vitro* from autologous cells, which are then re-transplanted), at long last, will produce the youthful, fully pigmented terminal scalp hairs that had fallen victim, for example, to the baldness-promoting activities of androgens.

Based on these beliefs, on the one hand, biotech companies with a focus on hair follicle neogenesis or stem cell–based hair loss therapy have been founded. On the other hand, hair transplant surgeons increasingly worry that their time-honored and effective surgical procedures for predictable hair restoration will soon become outdated, with hair transplant surgery slowly sliding down a relentless path towards ultimate extinction. The lay public, in turn, especially if aggrieved by a personal hair loss problem, and encouraged in this perception by mass media infatuation with anything that rings of stem cells and organ regeneration, is getting increasingly impatient with us physicians: "Why does it take you guys so long to just make new hair follicles pop up in the balding plate…?!"

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Yes, the pressure is on. Just the right time to lean back and to reflect, calmly and carefully: What are these much-reverberated views really based on? Do we actually need hair follicle stem cells and/or hair follicle neogenesis to successfully treat (or even cure) common hair diseases? Will hair restoration surgery really become replaceable in the foreseeable future?

In the following lines, I shall develop some personal, quite possibly controversial and provocative, arguments in response to these pertinent questions (for more background and some relevant references see, for example, Paus, R., *Drug Discov Today* 2006). The underlying views are those of a clinical dermatologist with roughly two decades of experience both in basic hair research and in treating patients with hair growth disorders.

Basic Facts of Hair Loss

For starters, let us recall a few simple facts about hair loss that must serve as the cornerstone for the discussion at hand:

1. By far, the far most common hair loss disorders in daily practice as well as in specialized alopecia clinics are androgenetic alopecia (of the male or female pattern variant), various causes of effluvium (the majority of which may represent telogen effluvium associated with androgenetic alopecia and/or thyroid abnormalities), and alopecia areata.

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2. All these forms of hair loss, at least in principle, are of a reversible nature. While this is widely recognized for alopecia areata and telogen effluvium, it is important that we also understand androgenetic alopecia as a—fundamentally—reversible condition. How else could one ever explain, for example, minoxidil-, finasteride-, cyclosporine A-, or ACTH overproduction-induced regrowth of hair in a balding scalp skin territory (more precisely: the re-transformation of vellus into terminal hair follicles by these agents)?
3. There is still no firm evidence that, even in very long-standing cases of androgenetic alopecia, the total number of hair follicles present per area of scalp skin declines more than marginally, if at all. Instead, these balding skin regions show massive, cosmetically undesired transformation of terminal into tiny vellus hair follicles. Essentially the same holds true for alopecia areata, where permanent hair follicle loss occurs as an extreme exception, if ever. To put it bluntly: In the vast majority of patients with even massive hair loss, there is essentially no loss of hair follicles! Thus, even when a follicle has become miniaturized beyond recognition by the naked eye, it still has the potential of retransformation and of generating large hair shafts.
4. There is no firm evidence whatsoever that there is anything basically wrong with the epithelial stem cells of vellus hair follicles in balding scalp skin regions, compared to those of non-balding or immediately adjacent terminal hair follicles. Recent meeting reports from the outstanding hair follicle stem cell laboratory of George Cotsarelis, in fact, suggest that vellus hair follicles have pretty much the same complement of epithelial hair follicle stem cells in the bulge region of their outer root sheath as large terminal ones. No one aware of points 2 and 3 will be surprised about this—how else could any vellus follicles ever make it back into the shiny world of terminal hair follicles if it had lost the epithelial stem cells that are an essential prerequisite for such an astounding miniorgan-transformation, and how else could they continue to engage in normal cycling patterns?
5. In stark contrast, patients with cicatricial (scarring) alopecia do have a major epithelial stem cell problem, and it is no surprise that this form of alopecia is notoriously irreversible. Here, both vellus and terminal hair follicles progressively lose their capacity to regenerate because their epithelial stem cells eventually suffer damage that is beyond repair. Alas, cicatricial alopecia represents a very small minority of all hair loss patients seen in clinical practice and, therefore, does not concern us in the current context.

Considering Stem Cell–Based Therapy

The simple facts above allow only one conclusion: The most common forms of hair loss (see 1) are not a stem cell problem, and have nothing wrong with the number of hair follicles available for hair shaft production. Therefore, one really wonders where the basic stem cell defect lies that supposedly "requires" correction by stem cell–based therapies. Why, then, should stem cells here be beneficial at all?

Two basic arguments are sometimes invoked to defend stem cell–based therapy of common hair loss disorders:

1. On the one hand, relatively crude mixtures of fairly undifferentiated epithelial cells that contain at least some stem cells, brought together with inductive fibroblasts, suffice for primitive hair follicles to self-assemble from appropriately self-sorted and aggregated cell populations in mammalian skin. Thus, hair follicle neogenesis appears deceptively simple (even though we are far from fully understanding the underlying molecular controls). On the other hand, it has proven rather difficult to reconvert vellus into terminal follicles in clinical practice (indeed, past pharmaceutical research has failed in generating highly efficient and reliable, long-lasting vellus-to-terminal converting drugs for safe clinical use, so that we are still stuck with two "children of serendipity"—finasteride and minoxidil—whose overall performance remains disappointing). Therefore, so this argument goes, let's just not fool around any longer with the hard and disappointing labor of trying to induce a vellus-to-terminal conversion. Instead, let us simply exploit stem cells to induce entirely new hair follicles! (And, who knows, maybe this will even stimulate neighboring vellus follicles to grow larger again?)
2. Maybe, if one somehow manages to increase the number of stem cells in the vellus follicles of balding scalp skin by some form of intracutaneous injection, the follicles will get bigger again and eventually can thus be reverted to their old, terminal splendor.

Argument 2 remains a theoretical possibility. However, precisely targeted delivery of such stem cell–based therapy to just the right area of tiny, unpigmented, and therefore hardly visible vellus follicles, surely must be fiendishly difficult (not to mention the associated regulatory nightmares for such cell-based therapy!). Also, if the epithelial stem cell compartment in a vellus follicle is fairly normal, anyway, and if Nature can so easily convert vellus into terminal follicles without evidence that it, first, has to engineer prior changes in the bulge, why do we need such therapy at all?

Much more likely, vellus-to-terminal hair follicle conversion would greatly be facilitated if we managed to identify agents that recruit more inductive fibroblasts from the hair follicle's connective tissue sheath into its dermal papilla (whose volume is thought to directly correlate with the volume of the hair matrix and, thus, with hair follicle size and hair shaft diameter). While it is conceivable that the injection of mesenchymal hair follicle stem cells might be beneficial for follicular dermal papilla enlargement, again, it is far from clear whether they (rather than ordinary, inductive connective tissue sheath fibroblasts) are really needed—not to mention the formidable technical difficulties of precisely targeted cell injection.

If you like argument 1 instead, you would probably also advocate buying a new house next door, rather than fixing the old one's broken front door, right…? Doesn't strategy 1 smack of "therapeutic overkill" to you? And are you not in-

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viting potential trouble that was definitely uncalled for (such as the theoretical risk of malignant degeneration of injected epithelial stem cells that have escaped normal controls and that, for example, give rise to basal cell carcinoma; or the production of ugly cysts or painful, chronically inflamed foreign body granulomata, instead of functional hair shafts)?

If all that doesn't worry you the least bit, what about the cosmetic results that you can expect? Remember: The beauty of terminal hair, to a large extent, lies in its luster, color, and durability, and in the symmetry and geometry of its arrangement, especially in the perfection of the alignment of hair shafts towards each other. Therefore, just forcing out of a balding plate a few miserable, malaligned hair shafts that, to top it off, more resemble scrotal hair than that of the beautiful forelock fancied by your client/patient, cosmetically, is unlikely to be a winning ticket…

Multiple investigators have, by now, impressively demonstrated in several elegant rodent models that hair follicle neogenesis is indeed possible, even in adult and aging mammalian skin. Therefore, I do not have any doubts that the iatrogenic induction of new terminal hair follicles in the balding and aging human scalp is possible, in principle. Yet, I still wait for at least theoretically convincing strategies to be put forward by the exponents of this "overkill" approach to alopecia management on how they will achieve (and, actually, guarantee) cosmetically acceptable hair beauty (i.e., perfect hair shaft alignment, geometry, cuticle structure, and arrangement) after successful folliculoneogenesis.

You see: Acidic drops of doubt are dripping into the optimistically sparkling "hair regeneration" claret that we are being toasted with so frequently these days, and we are left with the simple, initial question: Do we need follicle neogenesis for the management of common forms of alopecia at all?

Except for the exceptionally few patients with a completely "burned-out" form of cicatricial alopecia, or a congenital hair aplasia, I just fail to recognize why hair follicle stem cells (epithelial, mesenchymal) should be required, or might at least offer significant therapeutic benefit at acceptable cost and risk, in any of the common alopecias. The same goes for iatrogenic hair follicle neogenesis—a true wonder of applied developmental biology, but not a major new "cure" for hair loss disorders. Hair follicle–associated stem cells undoubtedly hold a lot in store for regenerative medicine—well beyond skin and the hair follicle—but they are not going to put hair transplant surgeons predictably out of business any time soon.

Of course, I have been wrong before, and may be wrong again…. And yet, in my view, if we ever wish to live up to the ancient, unmet therapeutic challenges posed to us by androgenetic alopecia, common causes of effluvium, and alopecia areata, we must labor on quite different frontiers: What is really needed is concerted and systematic research geared at developing efficient, predictable, and long-lasting

a. hair cycle control therapy,
b. stem cell protection therapy,
c. immune privilege restoration therapy,
d. exogen inhibition, and
e. vellus-to-terminal conversion by directing hair follicle fibroblast trafficking from the connective tissue sheath into the follicular dermal papilla.

But those are other stories, to be told in later issues of this *Forum*.

For now, suffice it to summarize: Classical hair restoration surgery has a future, and so does hair follicle stem cell therapy. But I predict that the latter's future does not lie in the management of common alopecias.✧

Editor's note: Ralf Paus received his medical degree from the Berlin Free University and served as a Postdoctoral Research Fellow in the Department of Dermatology at Yale University. He is currently Professor of Dermatology and Head of Experimental Dermatology at the University of Lübeck, Germany. Dr. Paus has authored over 250 peer-reviewed publications and is a world-renowned researcher in the fields of hair biology, regenerative medicine and neurobiology, neural endocrinology, and neuroimmunology of the skin. Dr. Paus is editor of the journal *Experimental Dermatology* and Section Editor of the *Journal of Investigative Dermatology*.